1 Title

2 Resting-state brain activity can predict target-independent aptitude in
3 fMRI-neurofeedback training

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39 Abstract

40 Neurofeedback (NF) aptitude, which refers to an individual's ability to change its brain
41 activity through NF training, has been reported to vary significantly from person to
42 person. The prediction of individual NF aptitudes is critical in clinical NF applications. In
43 the present study, we extracted the resting-state functional brain connectivity (FC)
44 markers of NF aptitude independent of NF-targeting brain regions. We combined the data

45 in fMRI-NF studies targeting four different brain regions at two independent sites
 46 (obtained from 59 healthy adults and six patients with major depressive disorder) to
 47 collect the resting-state fMRI data associated with aptitude scores in subsequent
 48 fMRI-NF training. We then trained the regression models to predict the individual NF
 49 aptitude scores from the resting-state fMRI data using a discovery dataset from one site
 50 and identified six resting-state FCs that predicted NF aptitude. Next we validated the
 51 prediction model using independent test data from another site. The result showed that the
 52 posterior cingulate cortex was the functional hub among the brain regions and formed
 53 predictive resting-state FCs, suggesting NF aptitude may be involved in the attentional
 54 mode-orientation modulation system's characteristics in task-free resting-state brain
 55 activity.

56

57 1. Introduction

58 Neurofeedback (NF) with functional magnetic resonance imaging (fMRI-NF) is a
 59 non-invasive method that modulates brain activity patterns through procedural learning.
 60 It is expected to be a promising method for elucidating the mechanisms of brain functions
 61 and treating the brain abnormalities of several neuropsychiatric disorders (Sitaram et al.,
 62 2017; Stoeckel et al., 2014; Thibault et al., 2018). A growing body of literature has
 63 suggested the efficacy of fMRI-NF treatment for major depressive disorder (Mehler et al.,
 64 2018; Takamura et al., 2020; Young et al., 2017a, 2017b), bipolar disorder (Paret et al.,
 65 2016), schizophrenia (Ruiz et al., 2013; Zweerings et al., 2019), post-traumatic stress
 66 disorder (Gerin et al., 2016), attention-deficit hyperactive disorder (Alegria et al., 2017),

67 anxiety disorder (Scheinost et al., 2013; Zilverstand et al., 2015), and Parkinson's disease
68 (Subramanian et al., 2011).

69 However, in terms of clinical usefulness, several issues remain with fMRI-NF,
70 especially since an individual's ability to change its brain activity through NF training,
71 referred to as 'NF aptitude' in this paper, significantly varies across individuals (Kadosh
72 and Staunton, 2019). The issue becomes more serious in the clinical application of
73 fMRI-NF because individuals who have insufficient NF aptitude will barely benefit from
74 fMRI-NF treatment. Changes in treatment are generally time-consuming and expensive.
75 Therefore, when fMRI-NF is used for clinical practice, before such treatment, predicting
76 whether each patient has sufficient NF aptitude is desirable.

77 The factors that define successful NF training can be broken down into individual
78 participant factors as well as such external factors as experimental conditions (Haugg et
79 al., 2020a; Sepulveda et al., 2016). Furthermore, individual aspects can be categorized
80 into demographic-psychological (Kadosh and Staunton, 2019) and biological factors in
81 which the neurobiological aspects are of our interest.

82 At present, the most extensive report on the predictions of individual NF aptitudes
83 based on brain activity is the work by Haugg et al. (2020b), they gathered a large dataset
84 from various types of fMRI-NF studies and tried to predict individual NF performances
85 based on brain activation during localizer tasks in each experiment. More preferably, we
86 wish to screen patients before NF training using a *task-free* setting, such as their
87 resting-states. To the best of our knowledge, only one study predicted the efficacy of NF
88 treatment/training based on resting-state FC (Scheinost et al., 2014). Unfortunately, it

only focused on the NF performance of a particular target brain region and the resting-state FC connected to it. Considering that the target region of fMRI-NF treatment depends on the target disease or its symptoms, it is more desirable to predict individual aptitudes of NF targeting an arbitrary brain region based on the activity of widely-distributed brain regions, as we successfully predicted the individual characteristics related to cognitive functions and clinical states by combining the whole-brain FC with a machine learning technique (Yamashita et al., 2018; Yoshida et al., 2017).

Motivated by this analogy, in the present study, we examined the feasibility that an approach that combines the resting-state FC in the whole brain with a machine learning method can predict individual target-independent NF aptitudes.

100

101

102 2. Materials and Methods

103 2.1. Participants

For this study's discovery dataset, 41 participants were recruited from the Hiroshima University Hospital, nearby medical clinics, or the local community. Among them, 35 participants had no history of mental or neurological disease. 22 participants had undergone neurofeedback training for left dorsolateral prefrontal cortex (DLPFC), and 13 for posterior cingulate cortex (PCC). The remaining six participants suffered from a major depressive disorder (MDD), had failed to respond to medication at least for four weeks, and underwent neurofeedback training for DLPFC.

110

111 For the test dataset, we recruited 24 healthy volunteers from the National Institute of
 112 Radiological Sciences, National Institutes for Quantum and Radiological Science and
 113 Technology. None had any history of neurological or psychiatric disorders. 16
 114 participants had undergone neurofeedback training for pregenual anterior cingulate
 115 cortex (pgACC), and the remaining eight for intraparietal sulcus (IPS). All participants
 116 provided written informed consent before joining the study, which was approved by the
 117 Hiroshima University Clinical Research Review Committee or the National Institutes for
 118 Quantum and Radiological Science and Technology Certified Review Board in
 119 accordance with the ethical standards established by the 1964 Declaration of Helsinki and
 120 its later amendments. The details of the demographic statistics for both datasets are
 121 summarized in Table 1.

122 All the participants completed the following identical procedure. After informed
 123 consent, they were administered BDI-II to evaluate their depressive symptoms outside of
 124 the MRI scanners. Next we acquired 10-minute (or 6-minute only for pgACC-1),
 125 eye-open resting-state fMRI, and structure MRI. During the resting-state fMRI scan,
 126 participants looked at a fixation point. The detailed scan parameters are displayed in
 127 Table 2. Following the resting fMRI session, participants underwent fMRI
 128 neurofeedback training. The procedures of the training session are described in the
 129 following section.

130

131 2.2. Neurofeedback training

132 2.2.1. General NF protocol

133 In all datasets, we administered fMRI neurofeedback training to manipulate brain
134 activity in a single region of interest (ROI) (Figure 1). On the feedback screen, the BOLD
135 signal values for the participant ROIs were displayed as line graphs, alternating between
136 blocks of up-regulation and down-regulation over the course of a single trial. The blocks
137 were indicated by background color. The number of neurofeedback trials/visits and
138 methods for defining the ROIs varied across the dataset. The following are the details of
139 the procedures of each dataset.

140

141 2.2.2. Group-specific NF protocols

142 **DLPFC-1:** Each participant underwent 5-day neurofeedback training on an
143 intermittent schedule over two weeks. On the first pre-training day, the resting-state fMRI
144 data were obtained prior to collecting the first structural MRI scan. The ROI was defined
145 as a 10-mm sphere at $x = -44$, $y = 4$, and $z = 24$ in the standard MNI brain. We used an EPI
146 localizer scan to fit the ROI to the individual brain space of each participant.
147 Neurofeedback training was composed of five baseline (rest) blocks (30 sec) and five
148 up-regulation blocks (30 sec). They attempted several strategies (e.g., mental calculation,
149 covert word operation) for increasing their neurofeedback signals during the
150 up-regulation blocks. Real-time fMRI processing and feedback presentation were
151 performed with Turbo-BrainVoyager™ version 3.2 (Brain Innovation, Maastricht,
152 Netherlands).

153 **DLPFC-2:** Each participant underwent 3 days of neurofeedback training on an
 154 intermittent schedule over one week. At the start of each NF session, participants
 155 completed a 2-back task as a functional localizer scan (Sherwood et al., 2016) from which
 156 we generated participant-specific ROIs. The ROIs were defined as the following overlap
 157 region: 1) task-related activation in the localizer 2-back task, 2) voxels with negative FC
 158 with the PCC during the resting state, and 3) the anatomical left DLPFC region adapted
 159 from the Brainvisa Sulci atlas (<http://brainvisa.info>). NF training was composed of four
 160 repetitions of a baseline (rest) block (48 sec) and an up-regulation block (48 sec).
 161 Participants were instructed to raise their signals in the up-regulation block over their
 162 signals in the baseline block. Real-time fMRI processing and feedback presentation were
 163 performed with a Turbo-BrainVoyager™ version 3.2. Participants completed four NF
 164 runs during each session.

165 **DLPFC-MD:** The patients with MDD participated in successive 5-day
 166 neurofeedback training. The ROI-making and neurofeedback training procedures were
 167 identical as the DLPFC-2 group, except for the number of neurofeedback runs completed
 168 in each session. The patients were asked to complete 1 run; if they wished to continue, up
 169 to two additional runs were performed.

170 **PCC:** Each participant underwent 5-day neurofeedback training on an intermittent
 171 schedule over two weeks. On each day, resting-state fMRI data were obtained before and
 172 after the neurofeedback training (although the data were ignored in this study). The ROI
 173 was defined as a 10-mm sphere centered at MNI coordinates: $x = -7$, $y = -49$, and $z = 28$.
 174 We used an EPI localizer scan to fit the ROI to the individual brain spaces of each

175 participant. Neurofeedback training was composed of five baseline blocks (30 sec) and
176 five down-regulation blocks (30 sec). The participants tried several strategies (e.g.,
177 concentration on body sensations) to decrease their neurofeedback signals during the
178 down-regulation blocks. Real-time fMRI processing and feedback presentation were
179 performed with Turbo-BrainVoyager™ version 3.2 and MATLAB® (Mathworks Inc.,
180 USA).

181 **pgACC-1:** Each participant underwent 4-day neurofeedback training on an
182 intermittent schedule over two weeks. We used a functional localizer scan designed to
183 efficiently locate in each participant the specific pgACC area that was most strongly
184 involved in the processing of negative affective information. In the 7-min localizer scan,
185 participants passively viewed happy or sad emotional faces. Following a localizer scan,
186 they engaged in neurofeedback training, which was composed of five down-regulation
187 blocks (32 sec) and five rest (baseline) blocks (32 sec). They tried several strategies to
188 increase their positive mood and used them during the down-regulation blocks to increase
189 the inverted neurofeedback signals. Online data analysis was performed using
190 Turbo-Brain Voyager™ version 3.2.

191 **pgACC-2 & IPS:** Participants were randomly assigned to either the pgACC or IPS
192 groups in a double-blinded manner such that the experimenters could not identify a
193 targeted ROI for a given participant. Each participant underwent 4-day neurofeedback
194 training on an intermittent schedule over two weeks. The neurofeedback training was
195 composed of the following: (1) rest (30 sec ×1), followed by (2) up-regulation blocks (30
196 sec ×8) and (3) down-regulation blocks (30 sec ×8). Participants tried to increase and

197 decrease their neural activities to match the inverted neurofeedback signals presented on
198 the screen. Although experimenters did not suggest any strategies, participants were
199 given hints that “positive” mood or thoughts may increase the signals, and “negative”
200 moods or thoughts might decrease them. Previously described anatomical ROIs were
201 specified as feedback targets: bilateral pgACC (7-mm radius sphere centered at MNI
202 coordinates: $x = 0$, $y = 46$, and $z = 4$; (Ito et al., 2017)) and left IPS (7-mm radius sphere
203 centered at MNI coordinates: $x = -42$, $y = -51$, and $z = 52$; (Young et al., 2017b)).

204

205 2.3 Neurofeedback aptitude scoring

206 To cope with the performance fluctuation over the sessions, we evaluated the
207 individual NF aptitudes in the following procedures. For each session, let $BOLD_t$ be a
208 BOLD signal averaged over the target ROI at the t -th time point. The signals were
209 centered and normalized based on robust Z scores during the baseline periods. The
210 normalized signals for the at the t -th time point were defined as

$$211 \quad z_t = (sign) \cdot (BOLD_t - median) / NIQR.$$

212 Here, *median* and *NIQR* are the median and the normalized interquartile range over
213 the BOLD signals during the baseline period: $\{BOLD_t; t \in (\text{baseline periods})\}$; and
214 (*sign*) is $+1$ if the condition of the neurofeedback training is for up-regulation or -1
215 for down-regulation. Using the normalized signals, the performance index for the s -th
216 session on the d -th training day was evaluated as the average over the up-regulation (or
217 down-regulation) periods:

$$P_{d,s} = \frac{1}{T_{\text{reg}}} \sum_{t \in (\text{reg})} z_t,$$

218 where (reg) denotes the set of the time points included in the up-regulation (or
219 down-regulation) periods in the session and T_{reg} is the total number of time points in
220 (reg). Subsequently, the daily performance for the d -th day, denoted by $\bar{P}_d$, was
221 summarized as the median of the performance indexes over all the sessions done on that
222 day. Finally, the individual NF aptitude scores for each participant were defined as the
223 mean over the daily performance of the last two days:

$$\bar{P} = \frac{\bar{P}_{D-1} + \bar{P}_D}{2},$$

224 where D is the NF training days assigned to the participant.

225

226 2.4 Functional connectivity

227 **Preprocessing.** The resting-state fMRI data were preprocessed using SPM12
228 (Wellcome Trust Centre for Neuroimaging, University College London, UK) on
229 MATLAB[®] as described in (Ichikawa et al., 2020; Nakano et al., 2020; Yahata et al.,
230 2016). The functional images were preprocessed with slice-timing correction, realigned
231 to the mean image, normalized and resampled in $2 \times 2 \times 2 \text{ mm}^3$ voxels, and smoothed
232 with an isotropic 6-mm full-width half-maximum Gaussian kernel. The potential
233 confounding effects (i.e., the temporal fluctuations of the white matter, the cerebrospinal
234 fluid, and the entire brain as well as six head motion parameters) were linearly regressed
235 out from the fMRI time series. Then a band-pass filter (0.008–0.1 Hz) was applied.

236 **ROIs selection.** A previous meta-analysis study reportedly found a common pattern
 237 of regional activation and deactivation during neurofeedback trials (Emmert et al., 2016).
 238 It determined 19 key brain regions of interest associated with NF. We predetermined the
 239 key regions of interest (ROIs) from Emmert et al. (ref, see Supplementary Table 1 for
 240 MNI coordinates). Of the 19 regions across the entire brain, we focused on a subset of 8
 241 ROIs (13 regions) due to the limitations of the computational resources and for the
 242 simplicity of the interpretation focusing on the putatively relevant key brain regions. For
 243 each individual, the time-courses of the fMRI data were extracted for each of the 13 ROIs
 244 (radius = 8 mm): bilateral anterior insular cortex (AIC), bilateral dorsolateral prefrontal
 245 cortex (DLPFC), bilateral temporal parietal junction (TPJ), bilateral intraparietal sulcus
 246 (IPS), precuneus (PCn), posterior cingulate cortex (PCC), bilateral posterior insular
 247 cortex (PIC), and right superior parietal lobule (SPL). These regions belong to major
 248 functional networks and are of specific concerns to fMRI neurofeedback (salience
 249 network, executive network, attention network, default mode network, auditory network)
 250 (Emmert et al., 2016).

251 **Assessing functional connectivity.** Pair-wise Pearson correlations among 13 ROIs
 252 were calculated to obtain a matrix of 78 FCs for each participant. We then averaged the
 253 bilateral FCs and finally reduced to 28 FCs consisting of 8 ROIs.

254

255 2.5 Prediction of individual's NF aptitude

256 To construct the prediction model of the individual NF aptitude scores (response
 257 variables) based on their corresponding resting-state FCs (explanatory variables) defined

258 in the previous sections, we applied partial least squares (PLS) regression (Chen et al.,
259 2009; Giessing et al., 2007; McIntosh et al., 2004, 1996; Wold, 1975; Yoshida et al.,
260 2017; Ziegler et al., 2013), which is more suitable for cases with high-dimensional
261 explanatory variables than ordinary least-square linear regression.

262 As possible sets of explanatory variables, we can consider in total $2^{28} = 268,435,456$
263 combinations among the 28 FCs we assessed in the previous procedure. To extract the
264 reasonable combinations to predict individual NF aptitudes, we adopted an exhaustive
265 search strategy (Figure 2). In this process, we trained a PLS model for every possible
266 combination using the discovery dataset collected at the Hiroshima University, and
267 evaluated its predictive performance by leave-one-out cross-validation (LOOCV): One
268 subject was used for validation data to evaluate the generalization ability of the PLS
269 model trained by the remaining subjects; and the procedure was repeated until all the
270 subjects were used as validation data. To cope with the high variability of individual NF
271 aptitudes, the prediction performance was evaluated by Spearman's correlation of true
272 NF aptitudes and predicted scores. We applied this procedure to all possible
273 combinations. Subsequently, we ranked the FCs in descending order based on their
274 frequency included in the best 100 combinations in terms of prediction performance to
275 determine the effective predictive factors for NF aptitude.

276 We also evaluated how accurately the PLS models classified the participants into
277 high-aptitude (participants whose NF aptitude scores exceeded the median) and the
278 low-aptitude groups (the other participants). To this end, the area under the curve of

279 receiver operating characteristic curve, abbreviated as AUC below, were calculated in the
280 LOOCV procedure.

281 Finally, we evaluated the prediction performance of the PLS models for the test
282 dataset collected in the National Institute of Radiological Sciences, National Institutes for
283 Quantum and Radiological Science and Technology, to demonstrate the generalization
284 ability for the independent NF protocols. Herein, the models were trained using all the
285 training datasets, and the prediction performance scores were identical as in the LOOCV
286 procedure (i.e. Spearman's correlation of the true NF aptitudes, and the predicted scores;
287 and AUC).

288

289 3. Results

290 First, we investigated the variability of the individual NF aptitudes among the
291 participants. The NF aptitude scores were distributed widely. Most participants (53/65)
292 showed higher NF aptitude scores than the baseline (=0) whereas approximately 18%
293 (12/65) of them were worse than the baseline. There were significant differences in the
294 NF aptitude scores between the PCC-targeting and several other groups (one-way
295 ANOVA with Scheffe post-hoc test (significance level 0.05)), but not between any other
296 pair except PCC-targeting group (See Supplemental figure 1). Regarding the dependence
297 on the depressive symptoms, the NF aptitude scores did not significantly differ between
298 the MDD patients (DLPFC-MD) and the healthy control (DLPFC-2) groups. Taken
299 together, the NF aptitude scores did not significantly depend on the depressive symptoms
300 or the NF protocols except the PCC-targeting protocol.

Next we trained and evaluated the PLS regression model to predict the NF aptitude scores based on the resting-state FCs according to the procedure explained in Sec. 2.5. As a result of LOOCV, the PLS model with the explanatory variables, which consist of six FCs (PCC-SPL, PCC-TPJ, PCC-IPS, PIC-TPJ, PIC-DLPFC, PIC-PCn), showed the highest Spearman's correlation between the predicted and true scores ($\rho = 0.477$, $p = 0.002$, see Figure 2). When the model classified the participants into the high- or low-aptitude groups, the ACU was 0.700 (Figure 2).

We then examined whether the PLS model with the highest performance in the LOOCV could predict NF aptitude scores in the test dataset in which the target ROIs were pgACC and IPS. The predicted NF aptitude scores still considerably correlated with the true scores ($\rho = 0.454$, $p = 0.027$, AUC = 0.660; Figure 3), where the resulting regression equation was given by

$$(NF\ aptitude) = 0.51 \cdot (PCC_SPL) + 0.20 \cdot (PCC_IPS) - 0.56 \cdot (PCC_TPJ) + 0.22 \cdot (PIC_TPJ) + 0.11 \cdot (PIC_DLPFC) - 0.18 \cdot (PIC_PCn) + 0.02. \quad (1)$$

Herein, “(x_y)” denotes an FC connecting two regions of “x” and “y.”

Since it might be possible that the best PLS model was too complicated to fit the dataset, we identified FCs that were robustly selected in highly-ranked PLS models through an exhaustive search. In fact, the regression coefficients for two FCs (PCC-SPL and PCC-TPJ) were more than double as much as the others. To examine the robustness of the FCs, we checked the explanatory variables used in the best 100 PLS models and found that the above six FCs appeared more frequently than the other FCs among those

models (Supplemental Figure 2). More interestingly, three FCs connected to PCC (PCC-TPJ, PCC-IPS and PCC-SPL) were always selected as the explanatory variables in the best 100 PLS models. Furthermore, the PLS model whose explanatory variables only consisted of those three FCs still showed a high prediction performance: $\rho = 0.437$, $p = 0.005$ and $AUC = 0.681$ in the LOOCV; and $\rho = 0.370$, $p = 0.076$ and $AUC = 0.632$ for the test dataset (Supplemental Figure 3), which are comparable to (but not better than) the best PLS model.

4. Discussions

In the present study, we examined the feasibility that individual's NF aptitudes independent of target brain regions can be predicted based on the resting-state FCs in the whole brain before NF training. The PLS model, which selected a small number of FCs as explanatory variables through a LOOCV using the training dataset, was successfully generalized to an independent test dataset. Such predictive screening is necessary for applying fMRI-NF to therapy situations. The present method demonstrated a preferable property in that the predictive screening could be achieved only by low-burden resting state fMRI scanning.

In the best PLS model, PCC and PIC were functional hubs connecting six ROIs that were selected as explanatory variables. Among them, it was notable that the FCs between PCC and other ROIs were robustly selected in the highly-ranked PLS models through an exhaustive search. PCC, which is a part of the default mode network (Buckner et al., 2008), plays an important role in self-oriented processing such as retrieving autobiographical memory or self-referential processing (Leech and Sharp, 2014). PIC is

345 related to interoceptive information processing (Craig, 2002). These functions may be
346 related to NF aptitude.

347 On the other hand, regions considered to be directly involved in control during NF,
348 such as DLPFC and AIC (Emmert et al., 2016), were not selected as hubs. This result
349 suggests that the active control of those regions during tasks is important, but not
350 reflected in connectivity in the task-free resting-state.

351 For comparisons with existing related studies, (Scheinost et al., 2014) and (Haugg et
352 al., 2020b) predicted the appropriateness of NFs from brain indices of resting-state FCs
353 and brain activity in the localizer tasks, respectively. In both studies, the brain indices
354 used for prediction corresponded to each NF target. On the other hand, our present study
355 demonstrated a feasibility that the NF aptitude of multiple target regions can be predicted
356 by the common brain indices. For example, even if we consider only depression, various
357 candidate targets (e.g. amygdala, insula, DLPFC) have been suggested (Linden, 2014).
358 Thus, the prediction model presented here might be used more widely than the existing
359 prediction models for specific NF targets. As a future prospect, it might be more clinically
360 valuable if a precise prediction of which types and targets of NF treatment are suitable for
361 an individual could be made from resting-state MRI alone.

362 A limitation of this study is that the number of the ROIs was restricted to enable an
363 exhaustive search for the selection of explanatory variables. It is possible that better
364 models could be created from whole brain networks with a larger number of nodes.
365 Methodologically, the development of automatic variable selection alternatives to

366 exhaustive searches is a future issue. In addition, more sites and within-subject
367 replications are also needed to reinforce the generalization ability.

368 Features other than resting functional images may also be useful in the predictions.
369 Examination using indices such as gray matter volume, cortical thickness, white matter
370 fibers, or neurotransmitters may be useful not only to construct better predictive models
371 but also to explore the neuroscientific basis of adaptation to NF training.

372

373 Acknowledgements

374 This research was supported by the Strategic Research Program for Brain Sciences
375 (Integrated Research on Depression, Dementia and Development Disorders) from the
376 Japan Agency for Medical Research and Development, AMED, Grant Numbers
377 JP20dm0107093, JP20dm0107094, and JP20dm0107096. This work was also partially
378 supported by JSPS KAKENHI Grant Numbers JP20K06874 and JP20H00625.

379

380 Data and code availability statements

381 The original data for this study will not be made publicly available due to the involvement
382 of patient data. It can be obtained upon request to the Department of Psychiatry and
383 Neurosciences, Hiroshima University, Japan (SY, yamawaki@hiroshima-u.ac.jp). IRB
384 imposing these restrictions on our data is Ethical Committee for Epidemiology of
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388

389

390 Competing interests

391 The authors declare that they have no competing interests.

392

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551

553 Figures

554

555 **Figure 1: Diagram of data acquisition procedure.** Participants underwent a resting-state fMRI
556 (rs-fMRI) scan and then participated in the following neurofeedback (NF) training sessions. From
557 the rs-fMRI data, a functional connectivity (FC) map, which is the synchronization between a set of
558 brain regions, was calculated and used as a feature of the individual's brain function. In the NF
559 training sessions, participants were asked to increase or decrease their brain activity displayed on the
560 feedback screen as a line graph. The degree of increase or decrease of the signal compared to
561 baseline in each session was quantified as the NF aptitude scores. Finally, a model was created to
562 predict the NF aptitude scores at the end of training from the FC map of the rs-fMRI sessions.

A Procedure to extract FCs and Model Training of Evaluation using **Discovery** data

563

564 **Figure 2: Training of the NF aptitude prediction model and extraction of the contributing**

565 **functional connectivities (FCs) using the discovery data.** (A) Schematic illustration of the

566 procedures of model training and FC selection. The PLS model was used for the prediction model.

567 All combinations connecting the eight pre-defined functional ROIs were tried one by one as the

568 possible explanatory variables of the PLS models, and their performances were evaluated through

569 LOOCV procedure in the discovery data. (B) NF aptitude scores predicted by the best PLS model in

570 LOOCV of the discovery data. The scatter plot shows the true (horizontal axis) and predicted

571 (vertical axis) NF aptitude scores validated over all runs in LOOCV. The blue markers indicate the

572 participants using DLPFC as a target region, and green markers indicate the participants using PCC.

573 Three different protocols in the NF targeting DLPFC were discriminated by three different marker

574 shapes. (C) ROC curve when the best PLS model was used as binary classifier to predict whether

575 each participant had high NF aptitude (with larger NF aptitude scores than the median in the

576 discovery dataset) or low NF aptitude (with lower NF aptitude scores).

577

A Model Training using **Discovery** data and Evaluation using **Validation** data

578

579 **Figure 3: Performance evaluation of the NF aptitude prediction model scores using the test**

580 **dataset.** (A) Schematic illustration of the model evaluation process using the test dataset. The NF

581 aptitude scores were predicted by the best PLS model determined in LOOCV. (B) The NF scores of

582 the validation data were predicted using the best combination of FCs in LOOCV in the discovery

583 data. The scatter plot shows the true (horizontal axis) and predicted (vertical axis) NF aptitude scores

584 tested in this process. The orange markers indicate the participants using pgACC as a target region,

585 and green markers indicate those using IPS. Two different protocols in the NF targeting pgACC are

586 discriminated by two different marker shapes. (C) ROC curve for the test dataset when the best PLS
587 model was used as the binary classifier to predict whether each participant had high NF aptitude
588 (with larger NF aptitude scores than the median in the test dataset) or low NF aptitude (with lower
589 NF aptitude scores).

590

591 **Figure 4: Selected functional connectivities as predictive factors for NF aptitude scores.**

592 Connectivity with positive relations with NF aptitude are colored in red and those with negative

593 relations are colored in blue. MNI coordinates of Z or X axes are noted. Numbers in the upper left

594 corners are regression coefficients in Equation (1). Abbreviations: posterior cingulate cortex (PCC);

595 superior parietal lobule (SPL); intraparietal sulcus (IPS); temporo-parietal junction (TPJ); posterior

596 insular cortex (PIC); dorsolateral prefrontal cortex (PFC); precuneus (PCn).

597

598 Tables

599 **Table 1: Demographics of participants in this study.** BDI-II: Beck Depression Inventory (Second
600 Edition).

Demographic attribute	Neurofeedback protocol						
	DLPFC-1 (N=12)	DLPFC-2 (N=10)	DLPFC-MD (N=6)	PCC (N=13)	pgACC-1 (N=9)	pgACC-2 (N=7)	IPS (N=8)
Gender							
Male	7	6	3	10	8	3	5
Female	5	4	3	3	1	4	3
Age (years)							
Range	21-51	21-24	25-51	20-28	20-39	21-38	21-37
Mean±SD	30.6±11.7	22.5±0.8	40.7±10.1	23.6±2.1	25.8±7.5	25.9±5.8	27.5±6.2
BDI-II							
Range	2-18	0-9	13-39	1-14	2-23	0-12	0-9
Mean±SD	7.1±4.6	4.1±3.2	28.7±9.4	6.6±3.8	6.0±6.6	6.9±5.6	2.8±3.2
Discovery dataset (N=41)				Test dataset (N=24)			

601

602 **Table 2: Parameters of MRI scanners.**

	Neurofeedback protocol						
	DLPFC-1	DLPFC-2	DLPFC-MD	PCC	pgACC-1	pgACC-2	IPS
MRI Scanner	Siemens MAGNETOM Verio 3.0T						
resting state fMRI							
scan time (mm:ss)	10:13	10:20	10:13	10:13	6:52	10:13	10:13
TR (ms)	1000	2000	1000	1000	2000	1000	1000
TE (ms)	30	30	30	30	25	30	30
flip angle (deg.)	80	62	80	80	90	80	80
voxel size (mm)	3.3 x 3.3 x 3.2	2.0 x 2.0 x 2.0	3.3 x 3.3 x 3.2	3.3 x 3.3 x 3.2	3.8 x 3.8 x 3.8	3.3 x 3.3 x 3.2	3.3 x 3.3 x 3.2
field of view (mm)	212	192	212	212	240	212	212
slice thickness (mm)	3.2	2	3.2	3.2	3.8	3.2	3.2
slice gap (mm)	0.8	0	0.8	0.8	0.456	0.8	0.8
slice number	42	69	42	42	33	42	42
T1w structure MRI							
scan time (mm:ss)	5:12	7:32	5:12	5:12	4:33	5:12	5:12
TR (ms)	2300	5000	2300	2300	2300	2300	2300
TE (ms)	2.98	2.88	2.98	2.98	1.98	2.98	2.98
flip angle (deg.)	9	4	9	9	9	9	9
voxel size (mm)	1.0 x 1.0 x 1.0	1.0 x 1.0 x 1.0	1.0 x 1.0 x 1.0	1.0 x 1.0 x 1.0	1.0 x 1.0 x 1.0	1.0 x 1.0 x 1.0	1.0 x 1.0 x 1.0
field of view (mm)	256	256	256	256	250	256	256
slice thickness (mm)	1	1	1	1	1	1	1
slice number	176	176	176	176	176	176	176
	Discovery dataset				Test dataset		

603

604 Supplementary materials

605 Supplemental Table 1: The ROIs selected in this study and their MNI coordinates. The ROI
606 names, their abbreviations, and their original ROI names used in the paper by (Emmert et
607 al., 2016). We used the identical coordinates as in their paper.

ROI name	Abbreviation	Name in (Emmert et al., 2016)	MNI Coordinates (x, y, z)
anterior insular cortex	AIC	anterior insular cortex	32, 26, 4 (R) -36, 20, -2 (L)
dorsolateral prefrontal cortex	PFC	dorsolateral prefrontal cortex	42, 0, 42 (R) -34, -4, 40 (L)
temporal parietal junction	TPJ	Temporo-parietal	62, -34, 34 (R) -58, -32, 32 (L)
intraparietal Sulcus	IPS	Parietal	30, -48, 40 (R) -30, -48, 38 (L)
posterior cingulate cortex	PCC	posterior cingulate cortex	8, -56, 38
precuneus	PCn	precuneus	0, -68, 24
posterior insular cortex	PIC	Temporal transverse	-36, -20, 16 (R) 38, -14, 18 (L)
superior parietal lobule	SPL	Parietal R	46, -68, 36

608

609

610 Supplemental Figure 1: Distribution of NF aptitude scores for each NF group. The asterisks
 611 (*) indicate the significant differences (significance level: 0.05, one-way ANOVA and Scheffe
 612 post-hoc test) between groups.

614 Supplemental Figure 2: List of functional connectivities (FCs) sorted in the descending order
615 of the frequency included in the best 100 prediction models. (Left) The list of FCs. (Center)
616 The indicators whether the FC for each row was used (black) or not (white). The horizontal
617 axis denotes the rank of the PLS model, based on the prediction performance in the LOOCV.
618 (Right) The frequency of FCs used in the best 100 PSL models.

619

Supplementary Figure 3: Prediction performance of the PLS model with only 3 FCs connecting PCC as the explanatory variables. The performance was evaluated by the LOOCV using the discovery dataset (Left) and generalization to the independent test dataset (Right). Upper panels: The scatter plot of the true (horizontal axis) and predicted (vertical axis). Lower panels: ROC curve when the best PLS model was used for the binary classifier to predict whether each participant had high NF aptitude (with larger NF aptitude score than the median in the corresponding dataset) and low NF aptitude (with lower NF aptitude score).